REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 43-50 are pending and under examination. Without acquiescence or prejudice, claim 43 is amended to particularly point out and distinctly claim certain embodiments of Applicants' invention. No new matter has been added by the amendment.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 43-45, 48, and 49 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* (*Regional Anesthesia and Pain Medicine.* 18:4, 1993) and Grond *et al.* (*Pain.* 79:15-20, 1999). Nickel *et al.* are alleged to expressly teach that flupirtine in combination with morphine not only enhances the analgesic effect of morphine, but also reduces morphine-induced tolerance, physical dependence and behavioral changes. The Examiner agrees that Nickel *et al.* do not specifically teach treatment of neuropathic pain, but asserts that Nickel *et al.* confirm their observations in cancer patients, and then asserts that Grond *et al.* teach that neuropathic pain is one of the major problems of cancer pain treatment. The Examiner then asserts that it would have been obvious to treat neuropathic pain with morphine and flupirtine.

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Perovic *et al.* (*Neurodegeneration.* 4:369-374, 1995). Perovic *et al.* are alleged to teach that flupirtine is a clinically safe compound that is non-sedating in most cases, from which the Examiner alleges that it would have been obvious to use flupirtine in combination with negligible amounts of morphine to avoid overt sedation.

C. Claim 47 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Devulder *et al.* The Examiner relies on Nickel *et al.* and Grond *et al.* as above, and then alleges that Devulder *et al.* teach the recited dosages of flupirtine *alone* for treating neuropathic pain.

D. Claim 50 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Cleary (*Cancer Control.* 7:120-131, 2000).

Cleary is alleged to teach that cancer pain has a neuropathic component, and further identifies certain of the specific cancers in claim 50.

Applicants respectfully traverse the rejections in sections A-D above, and submit that the instant claims satisfy the requirements of non-obviousness over the cited references. Mainly, it is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness for methods of using flupirtine and an opioid to treat *neuropathic pain*, specifically. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

The cited references fail to provide a reasonable expectation of success for methods of treating neuropathic pain. Instead, as recognized by the Examiner, Nickels *et al.* do not even mention *neuropathic* pain. At best, they suggest an enhanced effect for the combination of flupirtine and an opioid in treating *nociceptive* pain. However, as discussed below, the understanding in the art at the time of filing provides no technical basis to extrapolate from nociceptive pain to neuropathic pain; instead, it weighs against such an extrapolation by teaching that nociceptive pain and neuropathic pain have entirely different mechanisms. Accordingly, even assuming Nickels *et al.* suggest the claimed combination for nociceptive pain, this teaching, without more, fails to establish a reasonable expectation of treating neuropathic pain, as presently claimed.

Reading Nickels *et al.*, persons skilled in the art would *not* have reasonably expected the combination of flupirtine and an opioid to have any effect on neuropathic pain. Further to not even mentioning neuropathic pain, Nickels *et al.* fail to describe the specific type of art-accepted models that would have allowed extrapolation to neuropathic pain. Because of the unique mechanisms neuropathic pain, persons skilled in that specialized art typically relied, for example, on experimental rats specifically prepared using an induced peripheral nerve injury (*see, e.g.,* Bennett and Xie, *Pain*. 33:87-107, 1988; and Kim and Chung, *Pain*. 50:355-63, 1992, submitted herewith). These and other neuropathic pain models were well-known prior to the time of filing, as was the knowledge that neuropathic pain differs from other types of pain, illustrated not only by the reliance on such specialized models, but also by the need to develop pain scales specific to neuropathic pain (*see, e.g.,* Galer *et al.*, *Neurology*. 48:332-338, 1997,

abstract submitted herewith). Given the strong interest in treating neuropathic pain, if Nickels *et al.* had even remotely contemplated that possibility, then they would have most reasonably used or referred to an appropriate model. Instead, they used a rodent model of *nociceptive* pain. Hence, absent mention of an appropriate neuropathic pain model, the discussion of Nickels *et al.* would have had little or no relevance to neuropathic pain specialists, because, as noted above, such persons understood the unique mechanisms of this type of pain, and its independence from nociceptive pain.

Further, even the mention of treating cancer patients would not have reasonably allowed extrapolation to neuropathic pain, whether cancer-related or otherwise. First, cancer pain was known to have nociceptive or other components that differ from neuropathic pain, such as muscle spasms and inflammatory-type pain. Second, many cancer patients do not have neuropathic pain. Grond *et al.* illustrate both of these points. For one, Grond *et al.* show that cancer patients often have distinct types of pain, including nociceptive pain, mixed nociceptive/neuropathic pain, and neuropathic pain. By population, Grond *et al.* then demonstrate a relative ratio of about 64:31:5 of nociceptive:mixed:neuropathic pain in cancer patients (*i.e.,* only 32/593 cancer patients had neuropathic pain, and only 181/593 had mixed pain), showing that only a minority appear to have neuropathic pain. Statistically, Grond *et al.* therefore show that cancer patients do not *necessarily* have neuropathic pain.

In this light, if the Examiner were to allege that Nickels *et al. inherently* treat neuropathic pain, then Applicants submit that such an allegation would be unsupported by the technical evidence of record. To rely on an inherency theory, the burden of proof lies with the Examiner to provide extrinsic evidence that *makes clear* that the missing descriptive matter (*i.e.,* treating neuropathic pain) is *necessarily present* in the method of Nickels *et al.* *See* M.P.E.P. § 2112 (IV), citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Inherency may not be established by *probabilities* or *possibilities*, and the mere fact that a certain characteristic *may* occur or be present in the prior art is *not sufficient* to establish the inherency of that characteristic. *Id.* Here, according to Grond *et al.*, it is statistically less likely than otherwise for cancer patients to have neuropathic pain. Hence, even though neuropathic pain *may* occur, it is not *necessarily present* in cancer patients of Nickels *et al.* The teachings of Nickels *et al.* and

Grond *et al.* therefore weigh against any inherency in using flupirtine and opioids to treat neuropathic pain, whether in cancer patients or otherwise.

The deficiencies in Nickels *et al.* are bolstered by U.S. Patent No. 5,521,178 (submitted herewith), the corresponding patent to the studies in that abstract. Applicants can appreciate the difficulties in interpreting the limited teachings of an abstract, and the temptation to read more into such limited teachings than is warranted by the understanding in the art at the time of publication. However, a patent is often a different story, in part because Nickels and others would have had plenty of opportunity to explore different and even speculative possibilities, and to describe their experiments in greater detail. The *conspicuous absence* of any mention of neuropathic pain or even cancer pain in the '178 patent, combined with the use of animal models associated with *nociceptive* pain (*see* reference to Blake *et al.*, *Arz. Med. Exp.* 4, 146 (1963)), speaks to the patentee's (Nickels *et al.*) focus on nociceptive pain, and to the relatively limited scope of their teachings in the eyes of persons skilled in the art at that time. The *conspicuous absence* of their so-called "[i]nitial studies in cancer patients" also casts doubt on the credibility that would have been given to the abstract's discussion of such studies, given not only the strong interest and unfortunate lack of success at the time in treating neuropathic cancer pain, but also the knowledge that Nickels and others would have had plenty of opportunity to add these experiments to the application had they been successful. On this last point, the Nickels *et al.* abstract was published in July 1993, a few months *before* the October 1993 filing date of the U.S. non-provisional application that led to the '178 patent. The '178 patent thus further illustrates that Nickels *et al.* were focused on *nociceptive* pain, and strongly cautions against relying on that reference to establish any reasonable expectations of treating *neuropathic* pain.

Overall, because of their well-known mechanistic differences, it is respectfully submitted that the mere reference to nociceptive pain, even in cancer, is insufficient to establish a reasonable expectation of success in treating neuropathic pain, as claimed. It is also submitted that the other cited references fail to remedy the deficiencies in Nickels *et al.* and Grond *et al.* Applicants therefore submit that Nickels *et al.* and Grond *et al.* fail to establish the requisite

elements of a *prima facie* case of obviousness over the claimed methods of inducing an analgesic response to *neuropathic* pain.

Nonetheless, without acquiescence or prejudice, the instant claims have been amended to specifically recite the step of *selecting a mammal with neuropathic pain*. Because Nickels *et al.* do not remotely teach or suggest this active step, inherently or otherwise, nor do they provide any mechanistic reason to expect the combination of flupirtine and an opioid to successfully treat this *specific population* of mammals, it is respectfully submitted that a *prima facie* case of obviousness has not been established.

Secondary Considerations of Non-Obviousness

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, the patentability of the instant claims is strongly supported by secondary considerations of non-obviousness, which Applicants submit are sufficient to rebut any assumed *prima facie* case of obviousness.

Synergism as Evidence of Non-Obviousness. As here, synergism may point toward non-obviousness. *See* M.P.E.P. § 2141(I). As detailed below, Applicants submit that the synergistic effects of the presently claimed subject matter are greater than expected from the art to an unobvious extent, provide significant practical advantages in the treatment of neuropathic pain, and are commensurate in scope with the claims. *See* M.P.E.P. § 716.02(a), citing *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). It is also respectfully submitted that the practical advantages that follow from these synergistic effects would not have been expected from Nickels *et al.*, especially as they apply to patients with neuropathic pain, including those with *opioid resistant* neuropathic pain.

The combination of flupirtine and an opioid not only creates positive synergy in treating neuropathic pain, but does so without magnifying the otherwise overlapping negative side-effects of these two drugs. As discussed on the record, this combination synergistically enhances the analgesic activity of a given opioid dosage, without increasing sedation, a side-effect common to both agents. Goodchild *et al.* (*Pain Medicine*. 9:939-949, 2008) further illustrate these beneficial effects in humans. For instance, the treatments in Goodchild *et al.* significantly improve overall cancer pain scores (*see* Table 3; ranging from about 20-54%

improvement), but even more so, they *substantially* and therefore *selectively* improve neuropathic cancer pain scores (*see* Table 4; ranging from 40-798% improvement with most values far greater than 100%). These results not only support the synergistic and beneficial effects of the claimed combination in treating neuropathic pain, specifically, but also illustrate that general types of (nociceptive) pain differ mechanistically from neuropathic pain, as discussed above. As also discussed on the record, these synergistic effects can be achieved without a corresponding increase in negative side-effects, such as sedation. Given the well-known difficulties in identifying effective drug combinations that do not have magnified, dose-related side effects, Applicants submit that the synergism of the claimed combination clearly points toward the non-obviousness of that subject matter.

Applicants further submit that the synergistic and non-sedative properties of flupirtine in combination with an opioid are *unexpected*. First, the Federal Circuit as noted that in order to properly evaluate whether a superior property was unexpected, it should be considered what properties were expected. *Merck & Co. Inc. v. Biocraft Laboratories Inc.,* 874 F.2d 804, 808 (Fed. Cir. 1989). Here, Nickels *et al.* at best suggest an *additive* increase in analgesic activity for *nociceptive* pain. However, as discussed in greater detail above, the mere treatment of *nociceptive* pain whether additive or otherwise fails to establish any reasonable expectation of inducing an analgesic response to neuropathic pain, let alone a *synergistic* response.

There is also simply no technical reason to extrapolate from mere *additive* effects to *synergistic* effects, an apparent extrapolation made by the Examiner. For instance, the Examiner incorrectly states that Nickels *et al.* "teach the *synergism* with the same combination of morphine and flupirtine" (*see* the Action, page 9) (emphasis added). Applicants respectfully disagree, and submit that without more, a suggestion of "enhanced" effects does not automatically translate into an expectation of synergistic effects, especially for entirely different types of pain. To support this point, the instant situation clearly differs from that of *Ex parte The Nutrasweet Co.* (*Id.*), cited by the Examiner at page 7 of the Action of May 12, 2010. In that case, it was found by the Board that greater than additive effects would have been expected from the claimed combination because of *explicit* statements in the art to that effect; the *explicit*

statements were based on similar combinations of related molecules. Here, in contrast, the cited art (*e.g.,* Nickels *et al.*) simply provides no such statements, whether explicit or otherwise. Instead, it merely suggests an *additive* analgesic effect for nociceptive pain, which, from a technical perspective, differs significantly from suggesting a *greater than additive* analgesic effect for an entirely different type of pain.

There is also no technical or mechanistic reason to expect these synergistic analgesic effects *in the absence of overt sedation.* Rather, common technical sense suggests that when combining two agents with shared side-effects, such as sedation, somnolescence, nausea, hallucinations, etc., persons skilled in the art would have most reasonably expected the magnification of these side-effects (*see, e.g.,* Cleary, *Cancer Control*, *supra*). For example, even though adjuvant/opioid therapy has been recommended for pain, Cleary teaches that in his real-life experience of adjuvant therapy, "many patients...do not tolerate these medicines well and in fact *experience increased side effects*" (*see* page 127, column 2, last full sentence of Cleary) (emphasis added). As another example, Dionne achieved an additive increase in the analgesic effects of ibuprofen and opioids, *but at the expense of an increased incidence of adverse events* (*see* Dionne, *Journal of Oral and Faciomaxillary Surgery.* 57:673-678, 1999, abstract attached). As a third example, de Craen *et al.* (*BMJ.* 313:321–325, 1996, attached) found that multi-doses of a combination of paracetamol/codeine caused a significantly higher proportion of side effects compared to each agent alone. Hence, as noted above, persons skilled in the art understood the difficulties in identifying effective analgesic combinations that do not have magnified, dose-related side effects, and would have set their expectations accordingly.

Nickels *et al.* provide no technical reason to alter these expectations. Indeed, they do not even mention sedation, somnolescence, nausea, or similar side-effects. At best, Nickels *et al.* suggest that "flupirtine weakens morphine induced development of tolerance, physical dependence and behaviour changes." Persons skilled in the art, however, would have understood that Nickels *et al.* were *not* referring to sedation, because sedation has little to do with tolerance or dependence. Tolerance, for example, refers instead to the phenomenon whereby chronic exposure to a drug diminishes its antinociceptive or analgesic effect, or creates the need for a higher dose to maintain this effect. Also, sedation is typically not referred to as a "behaviour."

Instead, given the illustrative teachings of Cleary, Dionne, and deCraen, such persons would have most reasonably expected the sedative effects of flupirtine to *magnify* the sedative effects of the opioid. This expectation stands in direct contrast to Applicants' results, showing that flupirtine synergistically enhances the analgesic effects of opioids in neuropathic pain without causing or increasing sedation.

Overall, Applicants have described at least two *unexpected* and *superior* properties for the claimed combination of flupirtine and an opioid, specifically for treating *neuropathic* pain, as claimed. First, flupirtine synergistically enhances the analgesic activity of opioids in reducing neuropathic pain, and second, it does so without magnifying the dose-related sedative effects of these two agents. For neuropathic pain, Applicants therefore submit that synergistic results provided by the presently claimed combination are greater than those that would have been expected from the cited art to an unobvious extent.

The synergism of the claimed combination also provides significant, practical advantages in the treatment of neuropathic pain. As previously made of record, synergism between flupirtine and an opioid allows a therapeutically significant reduction (*e.g.,* 90% reduction) in the amount of either drug administered in order to obtain an analgesic effect, specifically for neuropathic pain. Accordingly, the claimed combination surprisingly renders analgesic an otherwise non-analgesic dose of an opioid, and can do so without sedation. Similarly, it can render effective an otherwise ineffective, non-sedative dose of an opioid. Certain practical benefits are also illustrated in Goodchild *et al.*, *supra*, where a number of later-stage cancer patients were able to substantially reduce their opioid usage when flupirtine was added to their treatment regime, and also significantly improve certain side-effects such as appetite – an important quality of life measurement. Applicants note that prior to this study, the patients were already receiving maximal opioid treatment without significant reduction in neuropathic pain, *i.e.,* they were essentially *opioid resistant*.

This last point illustrates an additional advantage, where synergism allows the treatment of otherwise *opioid resistant* neuropathic pain, such as that found in some cancer patients. Even if Nickels *et al.* were extrapolated to neuropathic pain, then mere additive effects would not have been expected to have a significant therapeutic effect on *any* type of opioid

resistant pain, let alone opioid resistant neuropathic pain. For illustration purposes, if morphine has essentially no effect on opioid resistant neuropathic pain, quantified as "zero," and if flupirtine still has some effect on opioid resistant neuropathic pain, quantified as "one," then a mere additive effect (0 + 1) from this combination would have been expected from Nickels *et al.* to provide little more than flupirtine alone – an effect of "one," or at best an effect that is only marginally greater than "one." Hence, for opioid resistant neuropathic pain, the greatest benefit that could have been expected from the combination of morphine and flupirtine (as per Nickels *et al.*) is essentially no benefit at all, or at least nothing beyond the use of flupirtine alone. In contrast, by unexpectedly showing that flupirtine synergistically enhances the analgesic activity of opioids so that the overall effect on opioid resistant neuropathic pain is meaningfully greater than "one," Applicants have opened up a variety of therapeutic options for an entire population of opioid resistant patients, who otherwise would been considered unable to benefit from such therapies. *See, e.g.,* Goodchild *et al.*, *supra*. Applicants therefore believe that the synergistic effects of the claimed combination are not only greater than expected, but provide significant, real-world benefits in the treatment of neuropathic pain.

In relation to these practical benefits, the Examiner, however, states that Applicants rely on certain features that are not recited in the claims (*e.g.,* 90% reduction in the amount of either drug to achieve an analgesic effect). Applicants respectfully disagree, and submit that they are not necessarily *relying* on these features, but are instead merely pointing out according to U.S. caselaw the "significant, practical benefits" that can be achieved by the synergistic effects of the claimed combination. *See, e.g., Ex parte The Nutrasweet Co., supra*. Applicants can find no rule that requires the claims to specifically recite these significant, practical benefits.

Applicants further submit that the unexpectedly superior properties discussed herein are commensurate in scope with the claims. On this point, Applicants would like to address the Examiner's remarks on the Declaration of Dr. Goodchild, where it is asserted that the data presented therein is not commensurate in scope with the claims. Specifically, it is stated that the Declaration "refer(s) only to the system described in the above referenced application and not to the individual claims" (*see* the Action, page 7). Applicants respectfully disagree, and

submit that they are aware of no rule that requires the Declaration to refer to the individual claims. Instead, Applicants understand that it should represent the subject matter that falls within the scope of those claims. Here, it is believed that the numerous flupirtine/morphine-based experiments described in the Goodchild Declaration and in the specification exemplify the effects of this combination in a variety of models of neuropathic pain, under a variety of representative conditions and dosages, and therefore correlate with the scope of the instant claims.

In summary, Applicants submit that the synergism discussed herein (and on the record) not only correlates in scope with what is now claimed, but is also greater than expected from the art to an unobvious extent, and further provides significant, practical advantages in the treatment of neuropathic pain. Applicants submit that the secondary considerations of non-obviousness are sufficient to overcome the alleged *prima facie* case of obviousness.

Applicants therefore submit that the instant claims satisfy the requirements of obviousness, and respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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Enclosures:

Goodchild *et al.*, *Pain Medicine*. 9:939-949, 2008.
Galer *et al.*, *Neurology*. 48:332-338, 1997, abstract.
U.S. Patent No. 5,521,178
Dionne, *Journal of Oral and Faciomaxillary Surgery*. 57:673-678, 1999, abstract.
de Craen *et al.*, *BMJ*. 313:321–325, 1996
Bennett and Xie, *Pain*. 33:87-107, 1988, abstract.
Kim and Chung, *Pain*. 50:355-63, 1992, abstract.

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